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REVIEW

Management of patients with hepatitis B in special populations

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Abstract

The development of effective nucleos(t)ide analogs (NAs) against hepatitis B virus (HBV) has improved the outcome of patients with chronic hepatitis B (CHB). This review updates issues related to the management of CHB patients included in special populations. Entecavir (ETV) and tenofovir (TDF) represent the currently recommended first-line NAs in patients with HBV decompensated cirrhosis. The combination of HBV immunoglobulin (usually for a finite duration) and NA is considered the standard of care for prophylaxis against HBV recurrence after liver transplantation. TDF is the best choice for hemodialysis patients and in patients with chronic kidney disease with nucleoside resistance. ETV and telbivudine are the preferred options in naïve renal transplant recipients and with low viremia levels, respectively. All hepatitis B surface antigen (HBsAg)-positive candidates should be treated with NAs before renal transplantation to achieve undetectable HBV DNA at the time of transplantation. Conventional interferon or NAs can also be used in children, on the basis of well-established therapeutic indication. Pregnant women at high risk of perinatal transmission could be treated with lamivudine, telbivudine or TDF in the last trimester of pregnancy. HBsAg-positive patients under immunosuppression should receive NA pre-emptively (regardless of HBV DNA levels) up to 12 mo after its cessation. In HBsAg negative, anti-HBc positive patients under immunosuppression, further studies are needed to form a final conclusion; however, it seems that anti-HBV prophylaxis is justified in such patients with hematological diseases and/or for those receiving rituximab-containing regimens, regardless of their anti-HBs or serum HBV DNA status.

Key words: Hepatitis B; Antiviral therapy; Tenofovir; Entecavir; Telbivudine

Core tip: The management of hepatitis B virus (HBV) infection in special populations is reviewed. HBV patients with decompensated cirrhosis should receive nucleos(t)ides analogs (NAs) before and after liver transplantation. The choice of NA for patients with chronic kidney disease, renal transplant candidates and

recipients depends on viremia levels, the severity of renal dysfunction and previous viral resistance. Children at the immune-active period may receive interferon or NAs. Pregnant women at risk of perinatal transmission should receive class B antiviral drugs or LAM. HBV patients receiving immunosuppressives should receive antiviral therapy based on HBV serological profile, HBV DNA detectability and intensity of immunosuppression.

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INTRODUCTION

More than half a million people with hepatitis B virus (HBV) infection die annually from complications of chronic hepatitis B (CHB), mainly the development of liver decompensation and/or hepatocellular carcinoma (HCC)[1]. Untreated patients with HBV decompensated cirrhosis (HBV-DeCi) have a 5-year survival rate of only 14%-35%[2]. The major breakthrough in the field of therapy of CHB patients is the implementation of oral nucleos(t)ide analogs (NAs). Should they be instituted according to the international guidelines, they will eliminate viral replication and l improve liver dysfunction and survival[2,3]. In fact, the newer NAs [*i.e.,* entecavir (ETV) and tenofovir (TDF)] are potent antiviral agents with a minimal or even nonexistent risk of resistance and, therefore, they represent the currently recommended first-line for the therapy of CHB[3].

In all phase Ⅲ pivotal trials, NA efficacy and safety was assessed in CHB patients recruited with strict inclusion criteria. However, in the "real world" daily clinical practice, there are remain many CHB patients, who, because of their particular characteristics, have been excluded from the registration trials. These CHB patients are generally referred to as special populations. Although, they may be in need of more urgent antiviral treatment, such as those with HBV-DeCi, their therapeutic manipulation is usually based on a relatively low degree of evidence (*e.g.,* expert opinion or non-randomized trials). Consequently the decision as to whether special populations with CHB need treatment or not, which NA suits them best and the need for other specific management options, require careful consideration.

The specific populations with CHB can be divided in several groups and subgroups, determined on various characteristics, such as age, severity of liver disease and events/cormorbidities that may change the natural history of HBV infection. The present review focuses on the most frequently seen special populations with CHB. These are patients with decompensated cirrhosis, liver transplant (LT) recipients; patients with chronic kidney disease (CKD) and renal transplant recipients; patients under immunosuppressive therapy or chemotherapy; and finally young patients and pregnant women.

CHB PATIENTS BEFORE AND AFTER LIVER TRANSPLANTATION

Before liver transplantation

CHB is a dynamic disease that can change over time, resulting in serious decompensation[4]. All patients with HBV-DeCi should be commenced on NAs, regardless of viral load and ALT activity. Several lines of evidence demonstrated that these agents were generally well tolerated in the long-term and they suppressed viral replication, preventing possible flares in disease activity and the occurrence of HCC[5,6]. Such patients could be selected for LT if they present hepatic dysfunction [Child-Pugh score (CTP) $\geqslant$ 7 or model for end stage liver disease (MELD) $\geqslant$ 10] and/or at least one major complication (ascites, variceal bleeding or hepatic encephalopathy)[7,8]. The application of NAs prompted a new era in LT of HBV-DeCi patients, because they reduced the rates of recurrence remarkably and improved their prognosis dramatically (survival rates up to 90% over 5 years after LT)[9]. While awaiting for LT, patients should be followed closely, at least every 3 mo, for virological response and potential virological breakthrough, by applying a sensitive polymerase chain reaction (PCR) assay[3,10]. All data suggest that an effective pretransplant anti-HBV therapy prevents post-transplant HBV recurrence[11]. hepatitis B surface antigen (HBsAg)-positive candidates treated with NAs could maintain undetectable HBV DNA, ameliorate liver function and present long term survival after LT[12-16]. Interestingly, liver function may improve to such an extent that some patients might not need transplantation at the end[17-23] (Table 1). The critical parameters affecting the outcome of patients with HBV-DeCi under antiviral agents have been controversial. The baseline severity of liver disease, expressed by the CTP score or the baseline bilirubin and creatinine levels[24], and the levels of viral load in which antiviral treatment is started, may be potential influencing factors. Antiviral therapy initiation at earlier stages is associated with better liver function recovery (Table 1).

Pretransplant mainstay therapy should be potent, with high-genetic barrier agents (*i.e.,* ETV or TDF monotherapy), which present long-term efficacy, very good virological responses, low resistance rates and result in reduction of liver fibrosis[10,25]. For example, a recent study showed that ETV administration in HBV-DeCi patients had a beneficial impact on mortality[26]: those treated with ETV for 24 wk presented greater reduction in ALT levels and MELD score, compared with those commenced on lamivudine. The critical weak point of ETV and TDF is

Table 1 Studies of nucleos/tide analogs in patients with hepatitis B related decompensated cirrhosis (adapted by Cholongitas *et al*[88])

Ref.	Number of patients	NA(s) used	1-yr data		Prognostic factors for the outcome
			↓ CTP score ⩾ 2, (%)	MELD score ↑	
Fontana *et al*[17]	154	LAM	NR	NR	Serum bilirubin and creatinine levels at baseline
Schiff *et al*[18]	226	ADV	NR	-2	NR
Shim *et al*[19]	70	ETV	49	-2.2	NR
Liaw *et al*[20]	45/45/22	TDF/TDF + FTC/ETV	26/48/42	-2/-2/-2	NR
Chan *et al*[21]	114/114	LdT/LAM	32/39	-1.0/-2.0	NR
Hyun *et al*[22]	45/41	ETV/LAM	NR/NR	-4.9/-3.7	Baseline CTP and MELD at 3 mo
Cholongitas *et al*[23]	52	ETV/TDF	23.8/19.3	-0.4/-2.2	Changes in MELD score between baseline and 6 mo

NA: Nucleos/tide analogs; ADV: Adefovir; CTP: Child-Turcotte-Pugh; ETV: Entecavir; TDF: Tenofovir; FTC: Emtricitabine; HBV: Hepatitis B virus; LAM: Lamivudine; LdT: Telbivudine; MELD: Model for end stage liver disease; NR: Not reported.

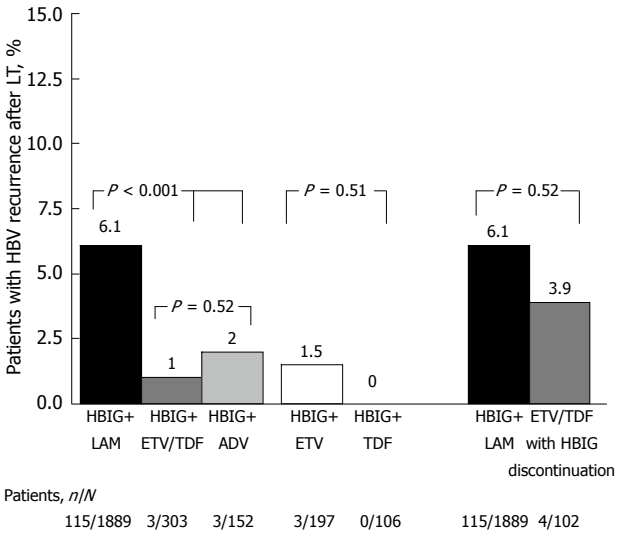

Figure 1 Risk of recurrent hepatitis B virus infection after liver transplantation in relation to the type of post-transplant hepatitis B virus prophylaxis[34,35]. HBIG: Hepatitis B immunoglobulin; LAM: Lamivudine; ETV: Entecavir; TDF: Tenofovir; ADV: Adefovir.

their higher cost compared with lamivudine and the potential TDF nephrotoxicity[27], although the latter was not confirmed in a recent randomized trial[20]. Similarly, lamivudine and telbivudine are limited by drug resistance, and adefovir is limited by its high cost, lower potency and slower onset of action[28]. However, clinicians should be aware that telbivudine can ameliorate creatinine clearance in patients with CHB[29,30] and could be effective in cases of moderate increase of viral load[31,32]. Other therapeutic NA options are the combination of emtricitabine plus TDF; however, this presents a similar efficacy to TDF or ETV monotherapy[20], but at a higher cost. Finally, pre-LT management should include surveillance of lifestyle factors, comorbid conditions and drug interactions[33].

After liver transplantation

In general, management after LT includes prophylactic and therapeutic approaches. Again, lamivudine is not considered an optimal first-line choice because of the elevated rates of viral resistance. In our review[34], the patients treated with HBV immunoglobulin (HBIG) and lamivudine had HBV recurrence more frequently compared with those commenced on HBIG and adefovir. More recently, we showed that the combination of HBIG and ETV or TDF is the best prophylaxis, almost eliminating post-transplant HBV recurrence (< 2%)[35] (Figure 1). Nevertheless, the high cost of HBIG and the fact that more and more patients undergo LT with undetectable HBV-DNA, has encouraged physicians to test either a shorter course of HBIG (with continuation of NA)[36,37], or HBIG-free prophylactic regimens with mono- or dual NA[35,38]. To select the appropriate group of LT recipients in whom HBIG withdrawal, or even no use at all, might be applicable, physicians should be aware of the risk of post-transplant recurrence. HBV DNA ⩾ 20.000 IU/mL and HBeAg positivity at the time of LT are associated with high risk of HBV recurrence, whilst HBV DNA clearance, as well as fulminant HBV and hepatitis D virus coinfection, pose less risk of HBV recurrence[39].

To date, the combination of an NA with a low dose of HBIG[34] is the preferred therapeutic regimen. Another option has been the use of vaccination instead of HBIG[40,41]. Active immunization with two courses of an accelerated schedule of double-dose recombinant HBV vaccine has been applied after LT. However, the results regarding patient response were conflicting, thus further studies are needed to confirm the application of this strategy in clinical practice.

Finally, regarding the use of liver grafts from anti-HBc positive donors, in our systematic review[42], we showed that these grafts can be used safely in HBsAg negative LT recipients. In these cases, anti-HBc/anti-HBs positive recipients may need no prophylaxis at all, while anti-HBc and/or antiHBs negative recipients should receive long-term prophylaxis with lamivudine (Figure 2).

The recurrence of CHB after LT is determined by the redetection of serum HBsAg and/or serum HBV DNA, which is usually connected with biochemical or clinical evidence of active liver disease. The treatment

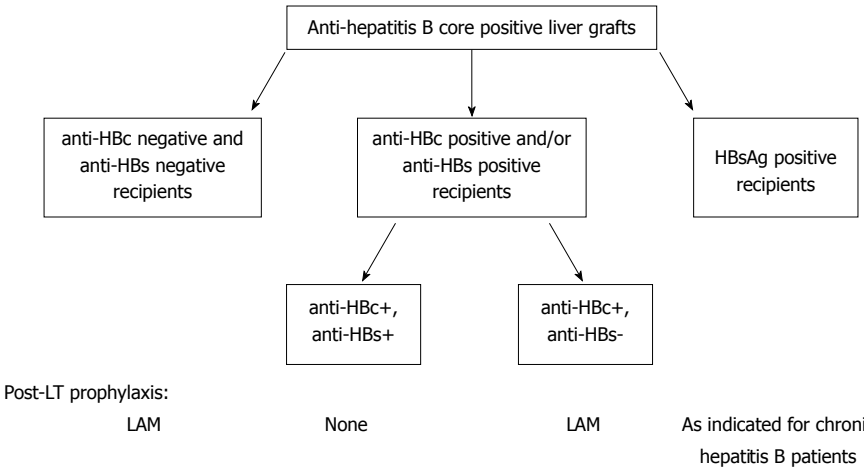

Figure 2 Proposed algorithm for allocation and management of anti-HBc positive liver grafts. Such grafts should be first offered to HBsAg positive, then to anti-HBc and/or anti-HBs positive, and ultimately to HBV naive (both anti-HBc and anti-HBs negative) recipients[42]. LT: Liver transplantation; HBIG: Hepatitis B immunoglobulin; LAM: Lamivudine.

Table 2 Dosage adjustment of nucleos(t)ides analogs in patients with chronic hepatitis B according to the creatinine (CrCl)[44]

CrCl (mL/min)	Lamivudine	Telbivudine	Adefovir	Entecavir[1]	Tenofovir
⩾ 50	100 mg/d	600 mg/d	10 mg/d	0.5 mg/d	245 mg/d
30-49	50 mg/d	600 mg/2nd day	10 mg/2nd day	0.25 mg/d	245 mg/2nd day
10-29	25 mg/d	600 mg/3rd day	10 mg/3rd day	0.15 mg/d	245 mg/3rd-4th day
< 5-10 or HD[2]	10 mg/d	600 mg/3rd-4th day	10 mg/wk	0.5 mg/wk	245 mg/wk[3]

[1]Recommendations only for nucleos(t)ide analog naïve patients (in lamivudine resistance the dosage is double); [2]In patients undergoing HD, all agents should be given once weekly after an HD session; [3]Only for patients on HD. HD: Hemodialysis.

of HBV recurrence depends on the NA that LT recipient was receiving before recurrence. TDF should be administered to patients with prior lamivudine resistance or to those receiving long term ETV[3,43] and the most potent combination of TDF and ETV should be used in patients with multidrug resistant HBV strains.

CHB PATIENTS BEFORE AND AFTER KIDNEY TRANSPLANTATION

Patients with CKD represent a very special population because of impaired immunity of renal failure, the many co-morbidities and the use of multiple medications[44]. They present a heterogeneous patient group, separated into three subgroups: patients with HBV-related nephropathies (membranous/membranoproliferative/IgA glomerulopathy/polyarteritis nodosa)[45-47], patients receiving hemodialysis (HD) and the renal transplant recipients. The course of CHB has a significant impact on the management of all these patient categories and affects their morbidity and mortality[48].

All HBsAg positive patients should undergo baseline renal evaluation, both before the start of antiviral treatment and during its administration. During long-term therapy, minimal rates of creatinine clearance decline have been reported with all NAs, except for telbivudine. Regular renal monitoring ensures prompt diagnosis and management of kidney disease, as well as adjustment of drug doses to renal function or if patients are on regular HD, after each session (Table 2)[3,44,49].

Patients receiving HD are high-risk individuals for CHB, because they are very susceptible to nosocomial transmission and occult HBV infection[50]. The latter might account for the potential risk of transmission during HD service and reactivation of HBV after renal transplantation (RT). Diabetes mellitus increased the possibility of occult HBV infection in patients on HD[51]. Vaccination is an essential component of preventive healthcare measures in this high-risk population, and it should not be underutilized because of poor response[52]. Special vaccination regimens are recommended, including double dose vaccination (40 mg each) in four doses, preferably applied before HD initiation. Serology should be performed every year, and a booster dose should be given if antibody titers are below 10 mIU/mL. Additional parameters complicating the diagnosis and the clinical course of CHB in patients on HD are the minimal or no increase in liver function tests[53], the lower viral load levels, because of its clearance by HD[54] and the high bleeding risk related to clotting disorders and intradialysis anticoagulant therapies. Thus, transjugular

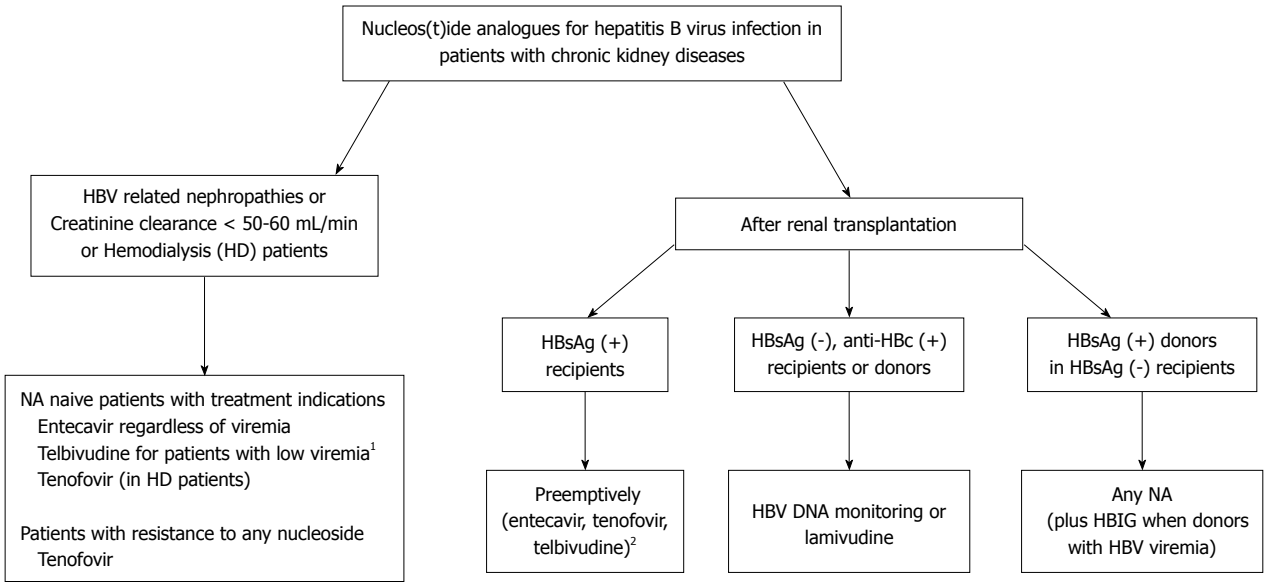

Figure 3 Proposed algorithm for the management of patients with chronic hepatitis B infection and kidney diseases. [1]Low viremia is considered as HBV DNA levels < 10^8 or < 10^6 IU/mL for HBeAg-positive and HBeAg-negative patients, respectively; [2]The choice based on similar criteria as before renal transplantation. NA: Nucleos(t)ide analogs; HBV: Hepatitis B virus; HBIG: Hepatitis B immunoglobulin[58].

liver biopsy in specialized centers and other non-invasive procedures, such as transient elastography, are the preferable option for fibrosis staging[55,56].

Antiviral therapy

With the advent of NAs, interferon (IFN) use has been limited to young patients with HBV-related glomerulopathy without cirrhosis, psychosis or autoimmune disease[57]. IFN has been poorly tolerated by patients with CKD, has shown relatively low efficacy and has set RT recipients under the risk of acute rejection[3], and thus, it is contraindicated.

Patients with HBV-related nephropathies, in which kidney disease is induced *via* the immune-complex, may respond highly to antiviral therapy[6], while those who need immunosuppressive therapy ideally should start antiviral treatment one month before treatment, continued for at least 12 mo after last dose of immunosuppressive drug[6]: ETV regardless of viremia, or telbivudine for patients with low viremia (*i.e.,* HBV DNA levels < 10^8 or < 10^6 IU/mL for HBeAg-positive and HBeAg-negative patients, respectively. However, ETV has low efficacy when there is lamivudine resistance; therefore, TDF should be used in that setting (Figure 3)[58].

Management of HBV patients with CKD requires special manipulation, a multidisciplinary approach and thorough renal monitoring. The administration of NAs has increased the prognosis of patients with CKD dramatically and has prevented the HBV recurrence after RT[3,59]. In patients with CKD and treatment indications for HBV infection, ETV is considered the first choice, regardless of viremia. Telbivudine is the best option when patients present low creatinine clearance and low viremia levels. Telbivudine has been proved efficacious in causing eGFR elevation in CHB patients with high risk of renal impairment[29,30]. TDF is the best choice during lamivudine resistance[58], but concerns exist regarding TDF use, because few cases of ostemalacia and Fanconi syndrome have been documented[60]. Physicians should be vigilant about these side effects and monitor patients closely who are under these medications, especially when creatinine clearance is below 50 mL/min.

Regarding patients on HD, antiviral treatment should be given to those with active or fibrotic liver disease and to renal transplant candidates. In general, RT offers higher survival and better quality of life in HBV positive patients on HD, with the condition that they would be under antiviral prophylaxis, since it is easier to prevent than treat CHB reactivation[61]. If no antiviral prophylaxis is administered after RT, immunosuppressive therapy would predispose the patients to rapidly progressive fibrosing cholestatic hepatitis, even if the underline liver disease was mild before RT[62]. Patients with HBV compensated cirrhosis are precluded from RT because they present high risk of hepatic decompensation after solitary RT, while patients with HBV-DeCi may only undergo combined liver and kidney transplantation[63]. In HD patients, ETV or TDF are considered first line agents, because of their high potency and the high genetic barrier to resistance[3]. Again, TDF is the first choice in lamivudine resistance[3,58] (Figure 3).

All HBsAg-positive RT candidates should be commenced on NAs before RT, regardless of the baseline liver histology and serum HBV DNA level[64]. NAs should be continued after RT to retain viral load clearance and prevent liver decompensation and fibrosis[3]. Oral antiviral treatment raised patient and

graft survival significantly; whereas a decade ago, HBsAg positivity was a significant predisposing factor for high mortality and graft loss[65,66].

The choice of the NA for HBsAg-positive RT is decided on an individual basis, according to the patient's HBV-DNA levels before transplantation and the previous exposure to NA(s). Lamivudine has been used extensively in this setting, but its results have been similar to those in other CHB populations. Thus, ETV, regardless of viremia and creatinine clearance, or telbivudine for patients with low viremia (*i.e.,* HBV DNA levels < 10^8 or < 10^6 IU/mL for HBeAg-positive and HBeAg-negative patients respectively) or TDF for cases with creatinine clearance > 60 mL/min (or history of resistance to lamivudine) could be proposed as the best choices (Figure 3). Although NAs should be continued lifelong after RT, there is a recent study showing safe antiviral withdrawal in four HBV positive RT patients who presented complete suppression of HBV infection having received antivirals for 14.3 mo. They remained negative for HBV DNA for a median 60.5 mo[67].

CHB IN CHILDREN

Most children remain at the immune-tolerant phase of CHB until late childhood or adolescence[68]. This phase is characterized by very high viral load, normal transaminase levels and lack of active disease in liver biopsy[68]. During the immune-tolerant phase, currently available treatments of CHB have no established benefit and should not be administered[68]. However, transaminase levels should be monitored every 6-12 mo in children who are at the immune-tolerant phase, because some will progress to the immune-active phase of CHB[69]. During the immune-active phase, viral load declines, transaminase levels increase and hepatic inflammation with potentially fibrosis develop[69]. According to current guidelines, children presenting HBV DNA levels ⩾ 2000 IU/mL at the immune-active period and persistently elevated alanine transaminase levels > 1.5 times the upper limit of normal [on at least two occasions over at least 6 mo in HBeAg(+) children or on at least three occasions over at least 12 mo in HBeAg(-) children] are potential candidates for treatment[68]. Liver biopsy should be considered at this point as well. Treatment is indicated in case of moderate or severe inflammation or fibrosis[68].

Regarding the choice of CHB treatment, small studies showed that treatment with conventional IFNα for 24 wk accelerates HBeAg clearance and antiHBe seroconversion[70-72]. Improvements in liver histology and increased rates of HBsAg clearance were also reported in IFNα-treated children[71,72]. High transaminase levels, low viral load and greater inflammatory activity in liver biopsy were associated with higher response rates to IFNα in a few studies[70].

Concerning NA(s), a pivotal randomized trial including 288 children with HBeAg(+) CHB, showed that treatment with lamivudine for 52 wk was well tolerated and induced a virological response (HBeAg clearance and undetectable HBV DNA) in 23% compared with 13% of children treated with placebo (P = 0.04)[73]. However, genotypic resistance to lamivudine developed in 19% of children treated with lamivudine at week 52[73]. In a more recent study including 106 adolescents (12-18 years-old) with CHB [91% HBeAg(+)], a 73-wk treatment with TDF resulted in a virological response in 89% of patients compared with 0% in patients treated with placebo (P < 0.001)[74]. ALT normalization occurred in 74% and 31% of patients treated with TDF and placebo respectively (P < 0.001)[74]. However, HBeAg clearance rates did not differ between the two groups[74]. Higher ALT levels and low viral load were associated with higher response rates to TDF treatment. TDF was safe and no patients developed resistance[74].

Current guidelines recommend a conservative management approach and careful treatment evaluation in children with CHB[3]. IFN is the agent of choice, while NAs are a second-line treatment[68]. IFN is approved for use in children ⩾ 1 year-old and is given thrice weekly at a dose of 6 MU/m^2 (maximum of 10 MU) for 6 mo[68]. In contrast, PEGylated IFN is not licensed for use in children with CHB[68]. Lamivudine and ETV are approved for use in children ⩾ 2 years old, adefovir and TDF for adolescents ⩾ 12 years old, whereas telbivudine is approved for adolescents ⩾ 16 years old[10,75]. Lamivudine is administered at a dose of 3mg/kg per day (maximum of 100 mg) once daily and the other NAs at the usual adult doses[10,75]. The optimal duration of treatment with these agents in children remains unknown[68]. Under current circumstances, treatment should be given for at least 6-12 mo after HBeAg seroconversion[75], and indefinitely in patients who do not achieve HBeAg seroconversion[75].

CHB IN PREGNANCY

All pregnant women should be screened for the presence of CHB[10]. CHB positivity does not affect the pregnancy outcome[76] and vice versa: pregnancy does not have an impact on CHB course or activity[77]. However, CHB flares occur in the post-partum period and might lead to HBeAg clearance[77].

IFN, lamivudine, adefovir and ETV are listed by the FDA as pregnancy category C drugs (*i.e.,* animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans), whereas telbivudine and TDF are pregnancy category B (*i.e.,* animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in humans)[3]. Accordingly, the treatment of women of reproductive age contemplating pregnancy and not presenting advanced fibrosis has to be postponed until post delivery[3]. In cases of

advanced fibrosis or cirrhosis, treatment is urgent, with PEGylated IFN representing the first line option, because of its finite treatment duration[3]. In women with no response to IFN or other contraindications, TDF is the treatment of choice, providing that it would be continued during pregnancy[3]. When pregnancy is confirmed in women who are on IFN or NA treatment other than TDF, treatment is discontinued if there is not advanced fibrosis or cirrhosis; if there is, it is continued with the substitution of current medication with TDF[3]. Where medications are withheld during pregnancy, close monitoring is needed because of hepatic flare risk[3].

Whether the NAs use in pregnancy prevents perinatal HBV transmission is an area of uncertainty. In CHB endemic areas perinatal transmission occurs in 70%-90% of children born from HBeAg(+) mothers[78]. It is well established that the risk of progression from HBV infection to CHB is highest (approximately 90%) in infants born from women with CHB compared with patients who are infected with HBV later in life[79,80]. The risk of perinatal HBV transmission is substantially reduced by the combined prophylaxis of HBV immunoglobulin and HBV vaccination[78]; however, it remains high in women with increased viral loads[81,82]. Indeed, perinatal transmission of HBV is observed in approximately 8%-9% of women with high viral loads (> 10^7-10^8 copies/mL), despite infant immunoprophylaxis[81,82]. In a meta-analysis[83] incorporating 15 randomized controlled trials (n = 1693 pregnant women), treatment with lamivudine started at the 28th gestational week was safe and reduced the risk of HBV transmission. However, lamivudine did not show an effect on HBV transmission in women with HBV DNA levels > 10^8 copies/mL[83]. In a more recent, open-label, uncontrolled study[81], treatment with telbivudine started at the 20th to 32nd gestational weeks and was not only safe, but also prevented all cases of HBV transmission in women with HBV DNA levels > 10^7 copies/mL. Interestingly, perinatal HBV transmission occurred in 8% of women treated only with HBV immunoglobulin and HBV vaccination but not telbivudine[81]. Observational studies[84] suggest that treatment with lamivudine or TDF during pregnancy does not increase the risk of major birth defects. Therefore, women with high viral loads (> 10^6 IU/mL) should be treated with lamivudine, telbivudine or TDF in the last trimester of pregnancy to reduce the risk of HBV transmission[3].

CHB PATIENTS UNDER CHEMOTHERAPY OR IMMUNOSUPPRESSION

After HBV exposure, the virus may persist in the liver and other extra-hepatic sites for long periods, posing a risk of reactivation in individuals who receive chemotherapy or immunosuppressive therapy[85]. Although the precise factors associated with risk of reactivation are not well understood[85,86], viral and host factors, as well as immunosuppressive therapy characteristics, are involved[87]. For example, high risk of HBV reactivation is associated with the use of rituximab. The latter is a monoclonal antibody against the CD20 receptor of B lymphocytes[86] and it is used alone or in combination with steroids or other regimens. Currently, rituximab is considered the optimal treatment for B cell lymphomas[88], but its use has been extended in several other hematological and non-hematological diseases.

In clinical practice, any type of immunosuppressive therapy can lead to HBV reactivation, in both HBsAg positive and HBsAg negative/antiHBc positive patients[85]. Thus, it is highly recommended that all candidates for chemotherapy and immunosuppressive therapy should be screened for the HBV (HBsAg and anti-HBc). In HBsAg-positive candidates, NA(s) should be received pre-emptively before immunosuppressive therapy, regardless of baseline HBV DNA levels and for 12 mo after its cessation[85,86]. According to the current guidelines, lamivudine can be used only in HBsAg-positive candidates with low HBV DNA (< 2000 IU/mL) and when a finite and short duration of immunosuppression is scheduled, otherwise the candidates should be protected with a new NA (*i.e.,* ETV or TDF)[3].

Although HBsAg negative/anti-HBc positive patients have significantly lower risk of HBV reactivation compared with HBsAg positive patients, there are many reports of HBV reactivation in these patients, because the prevalence of anti-HBc is higher than that of HBsAg[3]. However, no standard management to prevent HBV reactivation has been established in this setting. In our recent systematic review (unpublished data) including more than 3300 HBsAg negative/anti-HBc positive patients, the rates of HBV reactivation were significantly lower in patients with non-hematological than with hematological diseases (2.5% *vs* 7.8%, $P < 0.001$), as well as in those under rituximab free compared with rituximab-containing regimens (3.5% *vs* 7.9%, $P < 0.001$). Based on these findings, we concluded that anti-viral prophylaxis should be given in HBsAg negative/anti-HBc positive patients with hematological diseases and/or those who are going to receive rituximab-containing regimens, regardless of their anti-HBs and serum HBV DNA status. On the other hand, HBsAg negative/anti-HBc positive patients with non-hematological diseases and/or those who are going to receive rituximab free regimens seem to require anti-HBV prophylaxis only if they have detectable HBV DNA. Nevertheless, further studies are needed to form final conclusions, particularly in specific groups of patients, such as those with solid tumors under chemotherapy. Lamivudine seems to represent an effective option in these cases, and clinicians should

Table 3 Management of chronic hepatitis B in special populations

Special population	Management
Before and after liver transplantation	Before: entecavir or tenofovir (± telbivudine in the presence of renal dysfunction) After: HBIG plus entecavir or tenofovir (consider telbivudine in the presence of renal dysfunction)
Before and after kidney transplantation	Before: entecavir or telbivudine or tenofovir (Figure 3) After: entecavir or telbivudine or tenofovir in HBsAg(+) recipients [plus HBIG when HBsAg(-) recipients receive graft from HBsAg(+) donor with HBV viremia] (Figure 3)
Pregnancy	lamivudine, telbivudine or tenofovir in the last trimester of pregnancy when HBV DNA > 10^6 IU/mL
Children	Interferon or nucleos(t)ide analogue (check age of child)
Under immunosuppressive regimen	HBsAg-positive candidates: lamivudine when baseline HBVDNA < 2000 IU/mL and short period (< 12 mo) of immunosuppression; otherwise: ETV or TDF HBsAg-negative/anti-HBc positive candidates: (1) if baseline HBV-DNA detectable: as HBsAg-positive candidates; (2) otherwise: lamivudine only in hematological diseases or rituximab containing regimens

HBV: Hepatitis B virus; HBIG: Hepatitis B immunoglobulin; HBsAg: Hepatitis B surface antigen; ETV: Entecavir; TDF: Tenofovir.

continue anti-HBV prophylaxis and/or the follow-up of such patients for at least 12 mo after discontinuation of immunosuppression.

CONCLUSION

Significant progress in therapies for HBV infection has led to improvements in the management of CHB patients with decompensated cirrhosis and after LT. The former group should be treated with ETV or TDF, which may lead to stabilization or even improvement of liver disease and possible withdrawal from the waiting list for LT. After LT, the combination of HBIG (at least for a certain period) and ETV or TDF appears to be the most effective approach, while ETV and TDF seem to have no difference in their impact on renal function[36]. HBIG-free prophylaxis with a new NA needs further evaluation, while telbivudine should be considered in cases of renal dysfunction[89]. In HBV patients with CKD, new NAs are the best options to minimize the consequences of HBV infection, providing that their dosage is adjusted according to creatinine clearance and taking into account the potential nephrotoxicity and resistance profile. Thus, ETV and telbivudine, an agent with promising data showing improvement in creatinine clearance, seem to be the preferred choices in CHB patients with CKD, while TDF is considered the best option in patients with prior resistance to any nucleoside analog. Physicians should be aware that all HBsAg positive patients should be treated with NAs before RT to maintain undetectable HBV DNA and prevent hepatic decompensation after RT. In pregnant women with CHB, close monitoring is needed and in those with high HBV DNA (> 10^6 IU/mL); treatment with lamivudine, telbivudine or TDF in the last trimester of pregnancy is the preferred option to reduce the risk of HBV transmission. If an infected child ultimately develops CHB, antiviral treatment should not be started urgently, since most of them are in the immune-tolerant phase of the disease. All HBsAg-positive candidates for immunosuppressive therapy should receive NA(s) pre-emptively, regardless of baseline HBV DNA, up to 12 mo after cessation of immunosuppression. Finally, HBsAg negative/anti-HBc positive patients with hematological diseases and/or those who are going to receive rituximab-containing regimens, regardless of their anti-HBs and serum HBV DNA status, should be on anti-viral prophylaxis (Table 3).

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